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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/060,188	04/14/1998	DOMINIC P. BEHAN		9333

35133 7590 01/10/2006  
COZEN O'CONNOR, P.C.  
1900 MARKET STREET  
PHILADELPHIA, PA 19103-3508

EXAMINER

HOWARD, ZACHARY C

ART UNIT PAPER NUMBER

1646

DATE MAILED: 01/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Interview Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/060,188	BEHAN ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Zachary C. Howard	1646	

All participants (applicant, applicant's representative, PTO personnel):

- (1) Zachary C. Howard. (3) \_\_\_\_\_  
 (2) Quan L. Nguyen. (4) \_\_\_\_\_

Date of Interview: 08 November 2005.

Type: a) ☒ Telephonic b) ☐ Video Conference  
 c) ☐ Personal [copy given to: 1) ☐ applicant 2) ☐ applicant's representative]

Exhibit shown or demonstration conducted: d) ☐ Yes e) ☒ No.  
 If Yes, brief description: \_\_\_\_\_

Claim(s) discussed: NONE.

Identification of prior art discussed: NONE.

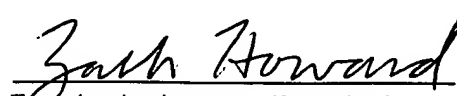
Agreement with respect to the claims f) ☐ was reached. g) ☐ was not reached. h) ☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: See Continuation Sheet.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

  
 Examiner's signature, if required

## Summary of Record of Interview Requirements

### Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record

A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

#### Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

#### 37 CFR §1.2 Business to be transacted in writing.

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,
- 2) an identification of the claims discussed,
- 3) an identification of the specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner,  
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

#### Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: The copy of the Office Action mailed 4/19/05 scanned into the IFW is unsigned. Applicants' representative was contacted. The copy of the Office Action mailed 4/19/05 received by Applicants was signed. At the time the Office Action was mailed, this case was still a paper case. Apparently only one of the two copies submitted by the Examiner was signed. The Examiner requested from Applicants a copy of the signed Office Action mailed 4/19/05 to have entered into the record. This copy is attached to this Interview Summary.

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### FACSIMILE

FROM: Quan L. Nguyen  
SENDER'S PHONE: 215.665.2158  
# OF PAGES (INCLUDING COVER): 34  
DATE: November 8, 2005  
TIMEKEEPER NO.: 2350  
SENDER'S FAX: 215.701.2057  
FILE NAME: AREN01.US2.CIP  
FILE #: 132947

RECIPIENT(S)	PHONE	FAX
Zachary C. Howard USPTO Art Unit 1646		571 273 2877

MESSAGE: Pursuant to your communications with Quan L. Nguyen regarding application serial number 09/060,188 filed April 14, 1998 please find attached a copy of the Office Action mailed April 19, 2005.

Carolyn Andress, Assistant to Quan L. Nguyen

IF YOU DO NOT RECEIVE ALL PAGES, PLEASE CALL [215.665.2000] or [800.523.2900] IMMEDIATELY.

THIS TRANSMISSION IS ALSO BEING SENT VIA:

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/060,188	04/14/1998	DOMINIC P. BEHAN		9333
35133	7590	04/19/2005		

COZEN O'CONNOR, P.C.  
1900 MARKET STREET  
PHILADELPHIA, PA 19103-3508

EXAMINER

HOWARD, ZACHARY C

ART UNIT PAPER NUMBER

1646

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

RECEIVED  
COZEN IP DEPT.

APR 22 2005  
DUE DATE 7-19-05  
MAX DATE 10-19-05  
DOCKETED BY m

# Office Action Summary

09/06/188

BEHAN ET AL.

Examiner

Art Unit

Zachary C. Howard

1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 27 March 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 34, 40 and 45-74 is/are pending in the application.
- 4a) Of the above claim(s) 71-74 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 34, 40 and 45-70 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 2/9/02
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: \_\_\_\_\_

Application/Control Number: 09/060,188  
Art Unit: 1646

Page 2

### DETAILED ACTION

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Zachary C. Howard, Art Unit 1646, Technology 1600.
2. Applicant's amendments filed 3/27/2003 are acknowledged. Claims 75 and 76 are canceled. Claims 69 and 70 have been amended. Claims 34, 40, and 45-74 are pending in this application. Claims 71-74 were withdrawn as drawn to a non-elected invention as set forth in the previous Office Action, mailed 11/19/2002.  
Claims 34, 40, and 45-70 are under consideration. This Office Action is in response to applicant's arguments filed 3/27/2003. The rejections of record can be found in the previous Office Action, 11/19/2002. New rejections apply as set forth herein.

#### ***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 34, 40 and 45-70 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. Claims 34, 40 and 45-70 are directed to methods of screening for agonists or inverse agonists of either an endogenous constitutive GPCR, or an endogenous GPCR subjected to constitutive activation, wherein location of said receptor in a mammalian tissue source is known and said receptor has been correlated with at least one mammalian physiological function and wherein an endogenous ligand for said receptor has not been identified.

A GPCR for which no ligand has been identified is hereafter referred to as an "orphan GPCR". No well-established utility exists for novel orphan GPCRs. The claims encompass any GPCR that has been "correlated with at least one mammalian physiological function", but this phrase is ambiguous in that it is broad enough to encompass many GPCRs wherein only the mammalian tissue source is known. Applicants state (on page 12) in the response of 3/19/03 that the phrase "correlated with at least one mammalian physiological function" refers to "a receptor that has, for example, been shown to expressed in a location that indicates its function." A function indicated by location of expression alone does not lend an orphan GPCR a substantial utility. For example, a GPCR expressed only in the brain could be said to be correlated with brain function, yet have no substantially utility. A substantial utility is a practical use which amounts to more than a starting point for further research and investigation, and does not require or constitute carrying out further research to identify or reasonably confirm what the practical use might ultimately be. For example, a method of screening for inverse agonists of a GPCR wherein constitutive activity of the GPCR is correlated with the onset of a particular disease condition would be a practical use of the material.



Application/Control Number: 09/060,188  
Art Unit: 1646

Page 3

However, a method of screening a GPCR wherein expression is correlated with "function in the brain" but has no particular correlation with a disease would not constitute a substantial utility. A stated belief that a connection exists between a GPCR and a disease, based solely on location of GPCR expression, is not sufficient information to use the claimed method to identify compounds to treat the disease; it merely defines a starting point for further research and investigation to determine if there is actually a nexus between the GPCR and the disease. Basic research, such as studying the properties of the claimed product or the mechanisms in which the product is involved, also does not constitute a substantial utility. In summary, the instant application has failed to provide information as to how one of skill in the art could use the claimed invention in a way that constitutes a specific or substantial utility, or a well-established utility. The proposed use of the claimed invention is simply a starting point for further research and investigation into potential practical uses of the claimed method.

**Note:** The previous rejection of claims 34, 40 and 45-70 under 35 U.S.C. § 112, first paragraph, for lack of enablement and for lack of written description is withdrawn in view of the new rejection under 35 U.S.C. § 112, first paragraph set forth below.

***Claim Rejections - 35 USC § 112, 1<sup>st</sup> paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34, 40 and 45-70 are also rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Even if a specific and substantial asserted utility or a well established utility were to be established, the claims which would then be enabling for -

1) a method of screening with a constitutively activated GPCR, wherein the GPCR has been constitutively activated by altering the third position removed from the beginning of the transmembrane domain represented by alignment with position 293 in the  $\alpha 1\beta$ -adrenergic receptor;

2) a method of screening with a constitutively activated orphan GPCR, wherein the orphan GPCR contains the sequence DRY in the second intracellular loop and is activated by mutating D to any other amino acid;

Application/Control Number: 09/060,188

Page 4

Art Unit: 1646

3) a method of screening with an constitutively activated orphan GPCR, wherein the orphan GPCR is constitutively activated by overexpression;

4) a method of screening with an endogenous constitutively active orphan GPCR or endogenous orphan GPCR subjected to constitutive activation, wherein the orphan GPCR has been "correlated with a physiological function" by correlation with tissue expression.

does not reasonably provide enablement for -

1) a method of screening with a constitutively activated orphan GPCR, wherein the orphan GPCR is constitutively activated by any other mechanism;

2) a method of screening with an endogenous constitutively active orphan GPCR or endogenous orphan GPCR subjected to constitutive activation, wherein the orphan GPCR has been "correlated with a physiological function" by any other correlation method.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

With respect to claims 34, 45-52, 61, 62, 63, 65, 67, and 69, the breadth of the claims is such that they encompass a method of screening with any endogenous orphan GPCR (correlated with a physiological function) that has been constitutively activated by any possible mechanism. Claims 45-52 recite limitations in the sequence of the GPCR to be used in the method, but no limitation is placed on the mechanism of GPCR activation. For example, claim 46 encompasses an orphan GPCR with the sequence X1BBHyX2, wherein X1 is a glycine and wherein the GPCR is constitutively activated by any mechanism.

Application/Control Number: 09/060,188

Page 5

Art Unit: 1646

Pages 38-53 of the specification discuss various means of constitutively activating different GPCRs with known ligands. All of these GPCRs and mechanisms are known in the prior art (see specification for references). These include the following mechanisms: mutational cassette (non-transmembrane or transmembrane), truncation of C-terminal tail, point mutations, anti-peptide antibodies, and overexpression. The majority of these mechanisms are specific to a particular species of GPCR. It is not predictable that these mechanisms will work with novel orphan receptors. For example, the specification details 8 non-transmembrane and 4 transmembrane mutational cassettes. Each cassette has been shown to work with a particular receptor. For example, the specification points to the FCSREKAA cassette, shown to constitutively activate  $\beta$ -adrenergic receptors. As evidence, the specification cites a review by Lefkowitz et al, 1993, that shows that mutations comparable to this cassette activate  $\beta 2$  and  $\alpha 2a$ -adrenergic receptors. The specification provides no evidence that this cassette will work to constitutively activate any other GPCRs other than adrenergic receptors. For each of the other eleven proposed cassettes, mutations corresponding to the cassette have been shown to constitutively activate a single GPCR. There is no evidence that any of these cassettes will activate any GPCR other than the one they have been shown to work with. In order to use this cassette to predictably activate orphan receptors, one of skill the art would first need to isolate to test a wide range of GPCRs to see whether or not use of this cassette results in constitutive activation of the receptors.

The examiner notes three mechanisms of constitutive activation of a GPCR that appear to predictably produce a constitutively activated GPCR:

- 1) Teitler et al (US Patent 6,255,089) teaches that constitutive activation of most GPCRs by mutation of the "third position removed from the beginning of the transmembrane domain" to any other amino acid, with changes to R, K, and E producing the greatest level of activation. This position corresponds to position 293 in the  $\alpha 1\beta$ -adrenergic receptor. Similarly, on page 45 of the instant specification, Applicant has provided 9 examples, all found in the prior art, of 9 receptors wherein mutation of an

Application/Control Number: 09/060,188  
Art Unit: 1646

Page 6

amino acid corresponding to position 293 of the  $\alpha 1\beta$ -adrenergic receptor resulted in constitutive activation of the receptor.

2) Scheer et al (February 1997. Proc Natl Acad Sci USA, 94: 808-813) teaches that the position E/DRY is highly conserved in GPCRs and mutation at the D position in the  $\alpha 1\beta$  or rhodopsin receptors results in constitutive receptor activation.

3) Pauwels (1998, Mol Neurobiol, 17(1-3): 109-135) reviews on pages 110-114 a large variety of GPCRs that have been constitutively activated by expression in recombinant systems with high levels of expression (overexpression).

None of Applicants' claims are limited to constitutive activation by any of these mechanisms. For example, the only limitation in claim 48 is that the receptor contain the sequence X1BBHyX2 in the 3<sup>rd</sup> intracellular loop, wherein Hy is alanine (A). Therefore, this claim encompasses receptors with the sequence X1BBAX2 in the 3<sup>rd</sup> intracellular loop that are constitutively activated by each the three mechanisms described above, but also by any other possible mechanisms. However, Applicant has not provided guidance as to what other mechanisms will predictably work to constitutively activate orphan GPCRs with X1BBAX2 in the 3<sup>rd</sup> intracellular loops. In order to use the full scope of the claimed invention, one of ordinary skill in the art would first need to test the other methods of constitutive activation in a number of receptors and determine whether or not the method predictably produces constitutive activity in a representative number of receptors. Without this information, one of ordinary skill in the art would not reasonably believe that the other methods would work to constitutively activate any orphan receptor.

It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification that the method of the present invention could be used with orphan GPCRs that are constitutively activated by any other method. There are no examples of using this method to screen orphan GPCRs that are constitutively activated by any other method. Thus the specification fails to teach the skilled artisan how to use the method as a screening agent without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the method for

Application/Control Number: 09/060,188

Page 7

Art Unit: 1646

the above stated purpose. Due to the large quantity of experimentation necessary to determine if the other mechanisms of constitutive activation could be used in the method for screening, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention. What Applicant has provided is a mere wish or plan and an invitation to experiment.

With respect to correlation with physiological function, all of the claims encompass a method of screening with an orphan GPCR (either endogenous constitutively active, or subjected to constitutive activation), wherein the orphan GPCR has been correlated with a physiological function. The phrase "correlated with physiological function" is broad and ambiguous and encompasses orphan GPCRs that have been correlated with physiological function by correlation with tissue expression, as well as by demonstration of an actual role in a physiological function.

Applicants provide no examples of orphan GPCRs that have been correlated with physiological function other than by correlation with tissue expression. Applicants have disclosed one GPCR, KSHV, which is constitutively active and has been correlated with a mammalian physiological function. However, at the time of filing of the instant application, several ligands that bound to KSHV had been identified (see page 347 of Arvankantis, et al, published January 23, 1997 in Nature, 385: 347-350). Applicants have also provided three examples of endogenous constitutively active orphan GPCRs; as described on pages 74-76 of the specification, these are GPR3 and two homologues, GPR6 and GPR12. However, Applicants do not correlate these constitutively active orphan GPCRs with physiological function other than by tissue expression (page 75), or provide teaching as how to correlate orphan GPCRs with physiological function by any means other than tissue expression. In order to practice the full scope of the claimed invention, one of ordinary skill in the art would first need to correlate an identified constitutively active orphan GPCR with a mammalian physiological function by means other than correlation with tissue expression. It is acknowledged that the level of skill of

Application/Control Number: 09/060,188

Page 8

Art Unit: 1646

those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification how to correlate an orphan GPCR with a physiological function, other than by tissue expression, without undue experimentation. For example, Uhlenbrook et al (Cellular Signaling. 14: 941-953. 2002) teaches ligands to GPR3, GPR6, GPR16, but is unable to determine the physiological role of these GPCRs; as Uhlenbrook teaches on page 951 "Basal expression of the respective receptors in HUVECs was low and no change (upregulation) could be observed, thus leaving the question for their physiological function unanswered. Gene knockouts and transgenic animals will be required to understand their physiological role." Therefore, even after a large quantity of experimentation, the physiological function of these GPCRs remains unknown and unpredictable, and a further large quantity of experimentation will be required to attempt to determine the physiological role of these GPCRs. Thus the specification fails to teach the skilled artisan how to use the claimed method over the full scope of the claims without resorting to undue experimentation.

In the response dated 3/27/2003, Applicants submit that the relevant question is not whether the specification lists such receptors, but rather whether it enables one of skill in the art to practice the invention of the claims without undue experimentation. Applicants submit that no evidence has been provided that those skilled in the art would be unable to correlate the receptor with at least one mammalian physiological function, or determine whether a receptor is known to have an endogenous ligand, and that each of these determinations are accomplished by experimentation that is routine. The examiner submits that the evidence provided by Uhlenbrook regarding the difficulty in determining the physiological function of orphan GPCRs (other than by tissue expression) is evidence that the experimentation is not routine, and therefore significant undue experimentation must be performed before the full scope of the claimed invention can be practiced.

Claims 34, 40 and 45-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application

Application/Control Number: 09/060,188  
Art Unit: 1646

Page 9

was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112, paragraph 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

With respect to claims 34, 45-52, 61-63, 65, 67 and 69, the claims encompass methods comprising constitutively activating an orphan GPCR by any possible mechanism. Therefore, these method claims are genus claims that encompass a large number of species of methods each comprising orphan GPCRs constitutively activated by any of a variety of mechanisms (discussed above in the enablement rejection). This genus is highly variant because a significant number of different approaches have been used to constitutively activate different receptors. Applicant has provided a variety of teachings for constitutive activation of individual species of GPCRs with known ligands. Applicant has not described constitutive activation of any orphan GPCRs. As noted above in the enablement rejection, three of Applicants teachings with regard to constitutive activation of GPCRs appear to so broadly applicable as to apply to orphan receptors. However, Applicants claims are not limited to the genus of methods encompassing only activation by these methods. Applicants' claims are instead drawn to a much larger genus that includes activation by any possible method, many of which have only been shown to work with a particular species of receptor with a known ligand, and there is no evidence that these mechanisms will work with any orphan GPCR. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the chemical structure of encompassed genus

Application/Control Number: 09/060,188

Page 10

Art Unit: 1646

of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of description for that broad class. The specification provided only the bovine sequence. Therefore, only methods comprising constitutive activation of orphan GPCRs by the three mechanisms detailed in the enablement rejection, but not the full breadth of the claims meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

All of the claims encompass a method of screening with an orphan GPCR (either endogenous constitutively active or subjected to constitutive activation), wherein the orphan GPCR has been correlated with any physiological function. The phrase "correlated with physiological function" is broad and ambiguous and encompasses a genus of orphan GPCRs that have been correlated with physiological function by tissue expression alone as well as those that have a demonstrated role in a physiological function. However, applicants have not provided any written description of a GPCR that has been correlated with physiological function by any means other than tissue expression. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

In the response dated 3/27/2003, Applicants submit that the written description requirement does not require Applicants to list a genus of orphan receptors with an associated physiological function. Applicants submit that what is required is that the



Application/Control Number: 09/060,188

Page 11

Art Unit: 1646

specification must reasonably convey to those of skill in the art the inventors were in possession of the claimed method of the invention.

The method of invention requires an orphan GPCR with a correlated physiological function other than by tissue expression. Without possession of said GPCR correlated with a physiological function other than by tissue expression, the method could not be practiced as claimed. The specification does not demonstrate possession of said GPCRs, and the specification and claims do not provide any guidance as to how to obtain said GPCRs correlated with physiological function other than by tissue expression. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

***Claim Rejections - 35 USC § 112, 2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34, 40, and 45-70 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 63 and 65 are indefinite because each claim depends from claim 69, and refer to "said mammal of step (d)", but there is no step (d) in claim 69.

Claims 64 and 66 are indefinite because each claim depends from claim 70, and refer to "said mammal of step (d)", but there is no step (d) in claim 70.

Claim 69 is indefinite because it is unclear how the inverse agonist or agonist is identified in step (b).

Application/Control Number: 09/060,188

Page 12

Art Unit: 1646

Claim 70 is indefinite because it is unclear how the inverse agonist or agonist is identified in step (b).

The remaining claims are rejected for depending from an indefinite claim.

**Note:** In view of Applicants' amendments to claim 70, the rejection of claim 70 under 35 U.S.C. § 103(a) over Gershengorn (US Patent 6,087,115) in view of Cesarman et al (US Patent 6,093,806) and Teitler et al (US Patent 6,255,089) is withdrawn and a new rejection of claim 70 under 35 U.S.C. § 102(e) over Gershengorn applies (see below). Applicants' arguments in regard to the Gershengorn reference are answered in the 102(e) rejection.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 40, 53, 55, 56, 58, 60, 68, and 70 are rejected under 35 U.S.C. 102(e) as being anticipated by Gershengorn et al (US Patent 6,087,115), published July 11, 2000 and filed January 22, 1997.

Claim 70 is drawn to a method for directly identifying a non-endogenous candidate compound as an agonist or inverse agonist to an endogenous constitutively active GPCR, wherein a location of expression of said receptor in a mammalian tissue source is known and said receptor has been correlated with at least one mammalian physiological function and wherein an endogenous ligand for said receptor has not been identified, said method comprising (a) contacting said compound with said GPCR and (b) identifying said compound as an inverse agonist or agonist to said GPCR.

Gershengorn teaches, in the section entitled "Detailed Description of the Invention" (column 3, line 29 to column 5, line 67) methods for screening constitutively active GPCRs for test substances that negatively antagonize the activity of the receptor. The GPCRs taught by Gershengorn include those that have been correlated with a physiological function, such as "GPCRs which are tumorigenic or which cause cells to

Application/Control Number: 09/060,188

Page 13

Art Unit: 1646

proliferate" (column 3, lines 48-50). As an example of a constitutively active GPCR that can be used in the method of the invention, Gershengorn teaches the GPCR of Kaposi's sarcoma associated herpesvirus (KSHV). The invention includes the steps of identifying the GPCR of interest (by determining it is constitutively active), identifying the signaling pathway by which it is active and a promoter responsive to such, expressing the GPCR and reporter protein in a host cell, and then screening various test substances for their effectiveness in acting as a negative antagonist of the GPCR. The method taught by Gershengorn does not require the ligand of the GPCR must be identified in order to practice the method. Gershengorn further teaches (column 5) that the test substances used in the screening method can be "traditional chemical compounds (such as benzodiazepines) or peptides." Benzodiazepines are non-endogenous chemical compounds. Gershengorn further teaches (column 5) that the test substances are "screened for their effectiveness as negative antagonists of a constitutively active GPCR." The instant application defines an inverse agonist (page 19) as "ligands which to the either the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonist." Agonists are not present in the method of Gershengorn, and the negative antagonists identified in the method lower the response of the constitutively activated receptor.

The method of Gershengorn meets the definition of "directly identified" as taught on page 18 of the instant specification, because the methods of Gershengorn do not include an agonist to the receptor.

Therefore, the method of Gershengorn meets all limitations of instant claim 70.

Claim 40 depends from claim 70 and recites the further limitation that the compound is determined to be an inverse agonist. As described above, Gershengorn teaches identification of negative antagonists, which meet the definition of an inverse agonists as taught in the instant application.

Claim 53 depends from claim 70 and recites the further limitation that the third intracellular loop of the receptor of step (a) comprises the sequence X1BBHyX2, wherein

Application/Control Number: 09/060,188

Page 14

Art Unit: 1646

X1 and X2 are each any amino acid; B is any basic amino acid; and Hy is any hydrophobic amino acid. Claim 53 encompasses loops that contain this sequence in either direction; therefore, the sequence could present in the amino acid sequence as read from the N-terminus to the C-terminus, or the C-terminus to the N-terminus. As shown in Figure 1 of Gershengorn, the third intracellular loop of KSHV contains the sequence RRKVR in the sequence as read from N-terminus to C-terminus, and the sequence KRRAD in the sequence as read from the C-terminus to the N-terminus. R and K are both basic amino acids and A and V are both hydrophobic amino acids. Therefore, each of the sequences meets the further limitation of claim 53, and the method taught by Gershengorn as applied to KSHV anticipates all of the limitation of claim 53.

Claims 55, 56 and 58 each depend from claim 53 and recite the further limitations that X1 is lysine (claim 55), that Hy is alanine (claim 56), or that X2 is arginine (claim 58). The KRRAD sequence described above contains a lysine at the X1 position and an alanine at the Hy position, and the RRKVR sequence described above contains an arginine at the X2 position. Therefore, these sequences clearly anticipate claims 55, 56 and 58 of the instant application.

Claim 68 depends from claim 70 and recites the further limitation that the mammalian physiological function to which the receptor has been correlated is an abnormal physiological function. The specification contains no limiting definition of an abnormal physiological function. Therefore, because KSHV (also known as human herpesvirus 8) is associated with tumors of humans, this receptor is correlated with abnormal physiological function and clearly anticipates claim 68 of the instant invention.

Claim 60 depends from claim 70 and contains the further limitation that the second intracellular loop of the receptor comprises the sequence XRY, wherein X is any amino acid other than aspartic acid, R is arginine and Y is tyrosine. The sequence of KSHV as shown in Sequence 1 (column 13) of Gershengorn contains the sequence VRY at positions 142-144. VRY meets the limitations of the sequence XRY and is located in the second intracellular loop of the receptor (see Figure 1). Therefore, this sequence clearly anticipates claim 60 of the instant application.

Application/Control Number: 09/060,188  
Art Unit: 1646

Page 15

Applicants argued in the response filed 3/27/2003 that the Gershengorn reference does not disclose an assay of the present invention, because 1) Claim 70 of the instant application requires that an endogenous ligand has not been identified for the constitutively active GPCR used in the method of screening, and Gershengorn identifies several ligands of the KSHV GPCR as demonstrated at Gershengorn, col. 8, line 26-29; and 2) Claim 70 recites that the candidate compound is directly identified, and Gershengorn only indirectly identifies a candidate compound, as demonstrated at Gershengorn, col. 8, lines 12-24.

Applicants' arguments with regard to Gershengorn have been fully considered but they are not persuasive for the following reasons: The general teachings of Gershengorn that encompass any constitutively active GPCR, including those correlated with physiological function, are described in columns 3-5 of Gershengorn. Nowhere in this section is it taught that the ligand to the constitutively active GPCR must be identified prior to using it in the method of the screening. Furthermore, based on the teachings of Gershengorn that the methods are practiced with a constitutively active GPCR, one of ordinary skill in the art would clearly recognize that ligand identification is not necessary to practice the methods taught by Gershengorn. While it is true that in the Examples section (col. 8, line 26-29) Gershengorn does determine several ligands that bind KSHV, this teaching does not detract from the obviousness of using a GPCR without first identifying a ligand in the general screening method taught by Gershengorn. The teachings of Gershengorn at col. 8, lines 12-24 are drawn to a portion of an Example wherein Gershengorn discloses the results of testing several ligands for binding KSHV. While these are tested indirectly, this teaching does not detract from the general teachings in columns 3-5 wherein negative antagonists of constitutively active GPCRs are screened directly with test compounds. This screening does not require an agonist to the receptor and meets the instant application's definition of "directly identified".

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Application/Control Number: 09/060,188

Page 16

Art Unit: 1646

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 34, 45, 49-51, 61, and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Teitler et al (US Patent 6,255,089) in view of O'Dowd et al (1995, Genomics, 28: 84-91.) Claim 69 is drawn to a method for directly identifying a non-endogenous candidate compound as an agonist or inverse agonist to an endogenous GPCR, wherein a location of expression of said receptor in a mammalian tissue source is known and said receptor has been correlated with at least one mammalian physiological function and wherein an endogenous ligand for said receptor has not been identified, said method comprising (a) subjecting said GPCR to constitutive activation, (b) contacting said compound with said GPCR and (c) identifying said compound as an inverse agonist or agonist to said GPCR.

Teitler teaches (column 4) that mutation in position 293 of the  $\alpha 1\beta$ -adrenergic receptor to any other of the 19 amino acids results in a constitutive receptor. Teitler further teaches (column 9, lines 7-23, and Figure 7) alignment of the  $\alpha 1\beta$ -adrenergic receptor with the serotonin receptors 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> in order to determine the equivalent position in each of these receptors. Teitler further teaches (Examples 1 and 2) that mutation of the equivalent position in either of the serotonin receptors also results in a constitutive receptor. Teitler further teaches "...the alignment methodology presented above should serve to permit the structural correlation between different receptors so that information gleaned from one receptor may be used to mutate another receptor. However, the evidence presently available suggests that the third position removed from the beginning of the transmembrane domain represented by position 293 in the  $\alpha 1\beta$ -adrenergic receptor seems to play a crucial role in the binding and activation of the coupled G protein, and that mutations introduced at that position alter the tertiary structure of the region." Teitler further teaches (for example, see column 18, lines 36-44) that the constitutively activated receptors can be used in a method of screening with non-endogenous compounds (e.g., mianseren or mesulergine) to identify inverse agonists.

Application/Control Number: 09/060,188

Page 17

Art Unit: 1646

Teitler further teaches (column 9) that for the  $\alpha 1\beta$ -adrenergic receptor, "the relative activity increased in the following order of amino acids "S, N, D, G, T, H, W, Y, P, V, L, M, Q, I, F, C, R, K, and E" and that "It is proposed that this order, with minor variations, exists for most G protein-coupled receptors due to the importance of the third position removed from the beginning of the transmembrane domain. A reasonable starting point for mutating the receptors should therefore involve mutation to one of the amino acids at the most active end of the above list."

Teitler does not teach using an orphan GPCR, wherein location of expression of said receptor in a mammalian tissue source is known and said receptor has been correlated with at least one mammalian physiological function, in the method comprising constitutive activation and screening for inverse agonists.

O'Dowd teaches a novel GPCR designated GPR8. O'Dowd further teaches (page 88) a mammalian tissue source of GPR8 in the human brain, specifically in the frontal cortex, and not in other regions. Therefore, the receptor is correlated with frontal cortex function, which is a physiological function. O'Dowd does not test GPR8 for ligand binding; therefore an endogenous ligand for GPR8 has not been identified. Therefore, GPR8 meets the definitions of an endogenous GPCR of claim 69. O'Dowd does not teach using this GPCR in methods comprising constitutive activation and screening for inverse agonists.

It would have been obvious to use the GPR8 taught by O'Dowd in the method comprising constitutive activation and screening taught by Teitler. The person of ordinary skill in the art would have been motivated to do so because, as Teitler teaches (column 2), "The importance of constitutively activated receptors to biological research cannot be overstated...the existence of constitutively activated receptors provides a novel screening mechanism with which compound which act to increase or decrease receptor activity can be identified and evaluated. Such compounds may become lead compounds for drug research." The person of ordinary skill the art would have expected success because Teitler teaches a method applicable to other GPCRs and teaches how to align other GPCRs with the  $\alpha 1\beta$ -adrenergic receptor.

Application/Control Number: 09/060,188

Page 18

Art Unit: 1646

As described above, Teitler teaches screening for inverse agonists, which meets the further limitation of claim 34.

The GPR8 sequence taught by O'Dowd (page 86, Figure 1) meets the further limitation of claim 45, because GPR8 contains the sequence RRKVT in the third intracellular loop, which meets the sequence definition of X1BBHyX2 of claim 45. This X1BBHyX2 is an endogenous sequence of the GPR8, which meets the further limitation of claim 61.

As described above, Teitler teaches mutating the third position prior to the transmembrane region preferentially to certain amino acids, of which R, K, and E are first chosen. This position corresponds to the T in the RRKVT sequence of GPR8, and therefore, the mutated receptor would meet the further limitations of claims 49, 50 and 51, wherein the receptor contains the sequence X1BBHyX2, wherein X2 is lysine (K; claim 49), X2 is arginine (R; claim 50); or X2 is glutamic acid (E; claim 51).

Claims 52, 62, 67, and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Teitler et al (US Patent 6,255,089) in view of Scheer et al (February 1997. Proc Natl Acad Sci USA, 94: 808-813) and in further view of Xu et al (1996. Genomics, 35: 397-402). Independent claim 69 is described above. Claim 52 depends from claim 69 and recites the further limitation that the 2<sup>nd</sup> intracellular loop of the receptor of step (b) comprises the sequence XRY, wherein X is any amino acid other than aspartic acid (D), R is arginine, and Y is tyrosine.

The teachings of Teitler are summarized above. Teitler does not teach a method of screening using an orphan GPCR subjected to constitutive activation, wherein the receptor comprises the sequence XRY.

Scheer teaches constitutive activation of a B-adrenergic receptor by mutation of a D residue in the DRY sequence. Scheer further teaches (page 808) that "the E/DRY motif ... is highly conserved among GPCRs (Fig1A)."

Xu teaches a novel GPCR designated OGR1. Xu teaches (Fig. 1) that the sequence of OGR1 is that of a GPCR and that the OGR1 has the DRY motif located in the 2<sup>nd</sup> intracellular loop of the protein. Xu further teaches that OGR1 was isolated by



Application/Control Number: 09/060,188

Page 19

Art Unit: 1646

RT-PCR of mRNA from an ovarian cancer cell line but expression of the gene is not found in normal ovary. Therefore, OGR1 is correlated with a physiological function in ovarian cancer.

It would be obvious to the person of ordinary skill in the art at the time the invention was made to substitute OGR1 for a serotonin receptor in the method taught by Teitler, and to further substitute constitutive activation by mutating position 293 for constitutive activation by mutating the DRY sequence. The person of ordinary skill in the art would be motivated to do so because the ligand of OGR1 is not known, and both position 293 and the DRY sequence are taught to be conserved in GPCRs, and in the absence of other evidence, mutating either one would produce a constitutively active receptor that would work equally well in the methods taught by Scheer. The person of ordinary skill in the art would have expected success because Scheer teaches that the DRY sequence is highly conserved in GPCRs.

The DRY sequence of OGR1 as taught by Xu is an endogenous sequence of OGR1, and therefore meets the further limitation of claim 62.

The teaching of Xu described above, that OGR1 is correlated with ovarian cancer, meets the further limitation of claim 67 that the physiological function is an abnormal physiological function.

### Notes

- a. The examiner has not found any art teaching endogenous constitutively active orphan GPCRs with a G at position X1 (claim 54); a lysine at position X2 (claim 57); or a glutamic acid at position X2, and thus these claims are not anticipated by or obvious over the teachings of Gershengorn et al described above.
- b. The examiner has not found any art teaching an orphan GPCR with a glycine at X1 (claim 46); a lysine at X1 (claim 47); or an alanine at Hy (claim 48) of the third intracellular loop, thus these claims are not anticipated or obvious over the teachings of Teitler et al described above. Further, the examiner has not found any art teaching

Application/Control Number: 09/060,188

Page 20

Art Unit: 1646

predictable constitutive activation of GPCRs by changing another residue in a GPCR to one of these residues, and thus these claims are not anticipated by or obvious over the prior art.

### **Conclusion**

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Application/Control Number: 09/060,188  
Art Unit: 1646

Page 20

predictable constitutive activation of GPCRs by changing another residue in a GPCR to one of these residues, and thus these claims are not anticipated by or obvious over the prior art.

### **Conclusion**


No claim is allowed.

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ROBERT S. LANDSMAN, PH.D.  
PRIMARY EXAMINER

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INFORMATION DISCLOSURE STATEMENT

In re Application of: Dominic P. BEHAN and Derek T. CHALMERS TECH CENTER 1600/2900  
 Serial No: 09/060,188  
 Filed: April 14, 1998  
 For: *A Method of Identifying Modulators of Cell Surface Membrane Receptors Useful in the Treatment of Disease*  
 Attorney's Docket: 3086-9  
 Examiner:  
 Group Art No:

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Honorable Commissioner of Patents and Trademarks, Washington D.C. 20231 on July 8, 1998.

*Suzannah K. Sundby*  
 Suzannah K. Sundby  
 Patent Agent for the Applicants  
 USPTO Reg. No. P-43,172

U.S. PATENT DOCUMENTS

Examiner's Initials	Cite No.	T <sup>1</sup>
	NA	

Examiner Signature	Date Considered

OTHER DOCUMENTS – NON-PATENT LITERATURE DOCUMENTS

Examiner's Initials	Cite No.		T <sup>1</sup>
3H		ALLA, S.A., et al (1996). Extracellular domains of the bradykinin B2 receptor involved in ligand binding and agonist sensing defined by anti-peptide antibodies. <i>J. Biol. Chem.</i> , 271, 1748-1755.	
↓		ADVENIER, C. et al (1992). Effects on the isolated human bronchus of SR 48968, a potent and selective nonpeptide antagonist of the neurokinin A (NK2) receptors. <i>Am. Rev. Respir. Dis.</i> , 146:5 Pt 1, 1177-81.	
✓		ALEXANDER, W.S., et al (1995). Point mutations within the dimer interface homology domain of c-Mpl induce constitutive receptor activity and tumorigenicity. <i>EMBO J.</i> , 14, 5569-78.	

Examiner Signature	Date Considered
<i>Jack Howard</i>	4/11/05

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	Examiner Zachary C. Howard	Art Unit 1646	Page 2 of 2

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